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(54) Title: NON-HUMAN TRANSGENIC ANIMALS DEFICIENT IN GAS6 FUNCTION AND THEIR USE

(57) Abstract: It has been shown that Gas6 deficient endothelial cells are resistant to activation by endotoxin and TNF- $\alpha$  *in vitro* and *in vivo* and that leukocytes did not or much less extravasate in Gas6 deficient mice. The present invention also relates to the manufacture of a medicament for the treatment of endothelial dysfunction. The present invention further relates to the use of an inhibitor of the Gas6 function and/or an inhibitor of a Gas6 receptor for the manufacture of said medicament.

WO 00/76309 A3

**A. CLASSIFICATION OF SUBJECT MATTER**IPC 7 C12N15/00 A01K67/027 A61K38/17 A61K39/395 //C07K14/745,  
A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A01K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

PAJ, BIOSIS, WPI Data, EPO-Internal, MEDLINE, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1999, no. 04, 30 April 1999 (1999-04-30) -& JP 11 000079 A (SHIONOGI & CO LTD), 6 January 1999 (1999-01-06) abstract  -/-	1-4



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

**\* Special categories of cited documents:**

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

11 December 2000

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21/12/2000

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## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 00/05318

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FRIDELL YIH-WOEI C ET AL: "GAS6 induces Ax1-mediated chemotaxis of vascular smooth muscle cells." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 12, 20 March 1998 (1998-03-20), pages 7123-7126, XP002154999 ISSN: 0021-9258 cited in the application page 7125, right-hand column page 7126, right-hand column abstract	5,6,8,9
X	NAKANO TORU ET AL: "Requirement of gamma-carboxyglutamic acid residues for the biological activity of Gas6: Contribution of endogenous Gas6 to the proliferation of vascular smooth muscle cells." BIOCHEMICAL JOURNAL, vol. 323, no. 2, 1997, pages 387-392, XP002155000 ISSN: 0264-6021 cited in the application page 389, right-hand column, paragraph 1 page 390, right-hand column, paragraph 3	5,7,10
X	O'DONNELL KRISTY ET AL: "Expression of receptor tyrosine kinase Ax1 and its ligand Gas6 in rheumatoid arthritis: Evidence for a novel endothelial cell survival pathway." AMERICAN JOURNAL OF PATHOLOGY, vol. 154, no. 4, April 1999 (1999-04), pages 1171-1180, XP000971169 ISSN: 0002-9440 abstract; figure 5	5,7-9

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-4

Non-human transgenic animal deficient in Gas6 function and its use.

2. Claims: 10; in part: 5-7

Use of an inhibitor of the Gas6 function for the manufacture of a medicament.

3. Claims: 8,9; in part: 5-7

Use of an inhibitor of a Gas6 receptor for the manufacture of a medicament.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box I.2

Claims Nos.: in part: 5-8

Claims 5-8 refer to an inhibitor of the Gas6 function and/or an inhibitor of a Gas6 receptor without giving a true technical characterization. Moreover, no such specific inhibitors are defined in the application. In consequence, the scope of said claims is ambiguous and vague, and its subject-matter is not sufficiently disclosed and supported (Art. 5 and 6 PCT).

No complete search can be carried out for such purely speculative claims whose wording is, in fact, a mere recitation of the result to be achieved.

Therefore, the search was limited to inhibitors which are either a soluble form of the AXL, MER or RSE receptor or a Gas6 antibody.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 00/05318

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 11000079 A	06-01-1999	NONE	